Pediatric Focused Safety Review: Invega® Extended-Release Tablets (paliperidone)

Pediatric Advisory Committee Meeting
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Office of New Drugs

Center for Drug Evaluation and Research
Food and Drug Administration

Outline

- Background Information
- Pediatric Studies
- Pediatric Labeling Changes
- Drug Use Trends
- Adverse Events
- Summary

Background Drug Information
Invega® (paliperidone)

- **Drug:** Invega® (paliperidone)
- **Formulation:** Extended-Release Tablets
- **Indications**:
  - Schizophrenia in patients 12 years and older
  - Schizoaffective disorder in adults (as monotherapy and an adjunct to mood stabilizers and/or antidepressant therapy)
- **Therapeutic Category:** Atypical antipsychotic agent

Background Drug Information, continued
Invega® (paliperidone)

- **Sponsor:** Janssen Pharmaceuticals, Inc.
- **Original Market Approval:** December 19, 2006
- **Pediatric Exclusivity Granted:** January 5, 2011
- **Pediatric Labeling Change:** April 6, 2011
- **Related Product:** Risperidone

Pediatric Written Request
Invega® (paliperidone)

- Indication: Schizophrenia
- Nonclinical Toxicology Study in juvenile rats
- Adolescents:
  - Pediatric Pharmacokinetic (PK) Study
  - Pediatric Efficacy and Safety Study
  - Pediatric Long-Term Safety Study

Relevant Nonclinical Toxicology Studies Invega® (paliperidone)

- Juvenile rats received oral paliperidone from postnatal days 24-73 of age
  - No adverse effects at plasma levels similar to expected exposures in adolescents.
  - Females: Impairment of performance in test of learning and memory seen at levels 3 times higher than expected exposures in adolescents. Reversible in recovery period.

Relevant Nonclinical Toxicology Studies, cont. Invega® (paliperidone)

- Juvenile dogs received oral risperidone for 40 weeks
  - Risperidone is metabolized to paliperidone.
  - Bone:
    - At plasma levels similar to those in pediatric patients receiving the maximum recommended human dose of risperidone, no adverse effects seen.
    - Decreased bone length and density seen at higher levels.
  - Delay in Sexual Maturation: Seen at all doses, including levels consistent with human exposures.
  - Females: Bone and sexual maturation effects showed little or no reversibility after a 12-week drug-free period.

Pediatric Pharmacokinetic (PK) Study Invega® (paliperidone)

- Open-label study to evaluate safety and PK of single-dose and multiple-doses of paliperidone
- 25 patients 10 to 17 years of age with schizophrenia or related disorders
- Results:
  - Peak plasma concentrations reached ~24 hours after single dose
  - Steady-state concentrations within 4-5 days of dosing

Pediatric Efficacy and Safety Study Invega® (paliperidone)

- 6-week, double-blind, placebo-controlled trial
- 149 adolescent patients (12-17 years of age) with schizophrenia received paliperidone (low, medium, or high doses). 51 patients received placebo.
- Dose range: 1.5 mg to 12 mg/day
- Primary endpoint: Mean change from baseline to endpoint in the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) total score.

Pediatric Efficacy and Safety Study, continued Invega® (paliperidone)

- Efficacy Results: Effectiveness shown for the 3 to 12 mg/day dose range, but no clear enhancement of efficacy at higher doses.

- Safety Results: Although adequately tolerated within 3 to 12 mg/day range, adverse events were dose related.

Pediatric Efficacy and Safety Study, continued Invega® (paliperidone)

- Safety Results, continued:
  - No fatalities
  - 4 patients experienced treatment-emergent serious adverse events in the paliperidone groups
    - Schizophrenia (n=2)
    - Agitation (n=1)
    - Mallory-Weiss syndrome (n=1)
  - 1 patient in the placebo group experienced a serious adverse event
    - Psychotic disorder

Pediatric Long-Term Safety Study - Ongoing Invega® (paliperidone)

- 2-years, open-label, safety trial of paliperidone (1.5-12 mg/day)
- Adolescents with schizophrenia
- Results as of cut-off date (September 8, 2010):
  - 399 patients with schizophrenia received ≥ 1 paliperidone dose
  - No fatalities
  - The most common serious adverse event was schizophrenia

Pediatric Labeling Changes Invega® (paliperidone)

- **1.1 Indications and Usage, Schizophrenia**
  - States that the efficacy of Invega® in schizophrenia was established in three 6-week trials in adults and one 6-week trial in adolescents, as well as one maintenance trial in adults.
- **2.1 Dosage and Administration, Schizophrenia**
  - Provides adolescent dosing information

Pediatric Labeling Changes, continued
Invega® (paliperidone)

- **5.6 Warnings and Precautions, Metabolic Changes**
  - Invega® labeling provides metabolic data from the study in adolescents with schizophrenia: changes in fasting glucose and lipids, mean change in body weight, and proportion of subjects with ≥7% gain in body weight.
    - In general, dose-related trends in hyperglycemia, dyslipidemia, and weight gain were seen in adolescents, consistent with adult data, and atypical antipsychotics as a class.

Pediatric Labeling Changes, continued
Invega® (paliperidone)

- **6 Adverse Reactions**
  - **6.1 Overall Adverse Reaction Profile**
    - States that safety was evaluated in 150 adolescents with schizophrenia who received Invega® 1.5-12 mg/day in the 6-week trial
  - **6.2 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia in Adults and Adolescents**
    - Lists adverse reactions reported by ≥2 % of adolescents including extrapyramidal symptoms

Pediatric Labeling Changes, continued
Invega® (paliperidone)

- **6 Adverse Reactions**
  - **6.4 Discontinuations Due to Adverse Reactions**
    - States that among the adverse reactions in the adolescent trial, only dystonia led to discontinuation (<1% of Invega® treated patients)
  - **6.5 Dose-Related Adverse Reactions**
    - Tachycardia, akathisia, extrapyramidal symptoms, somnolence, and headache

Pediatric Labeling Changes, continued
Invega® (paliperidone)

- **6 Adverse Reactions**
  - **6.7 Extrapyramidal Symptoms (EPS)**
    - States that the incidences of EPS-related adverse events in the adolescent trial similar to adult trials
    - There were higher incidences of dystonia, hyperkinesia, tremor, and parkinsonism in the adolescents

Pediatric Labeling Changes, continued
Invega® (paliperidone)

- **8.4 Use in Specific Populations, Pediatric Use**
  - Summarizes the results of the adolescent study
  - States that safety and effectiveness not established for the treatment of:
    - schizophrenia in patients <12 years of age
    - schizoaffective disorder in patients <18 years of age
  - Describes adverse findings of juvenile rat study with oral paliperidone and juvenile dog study with oral risperidone
  - States that the long-term effects on growth and sexual maturation have not been fully evaluated in children and adolescents

Pediatric Labeling Changes, continued
Invega® (paliperidone)

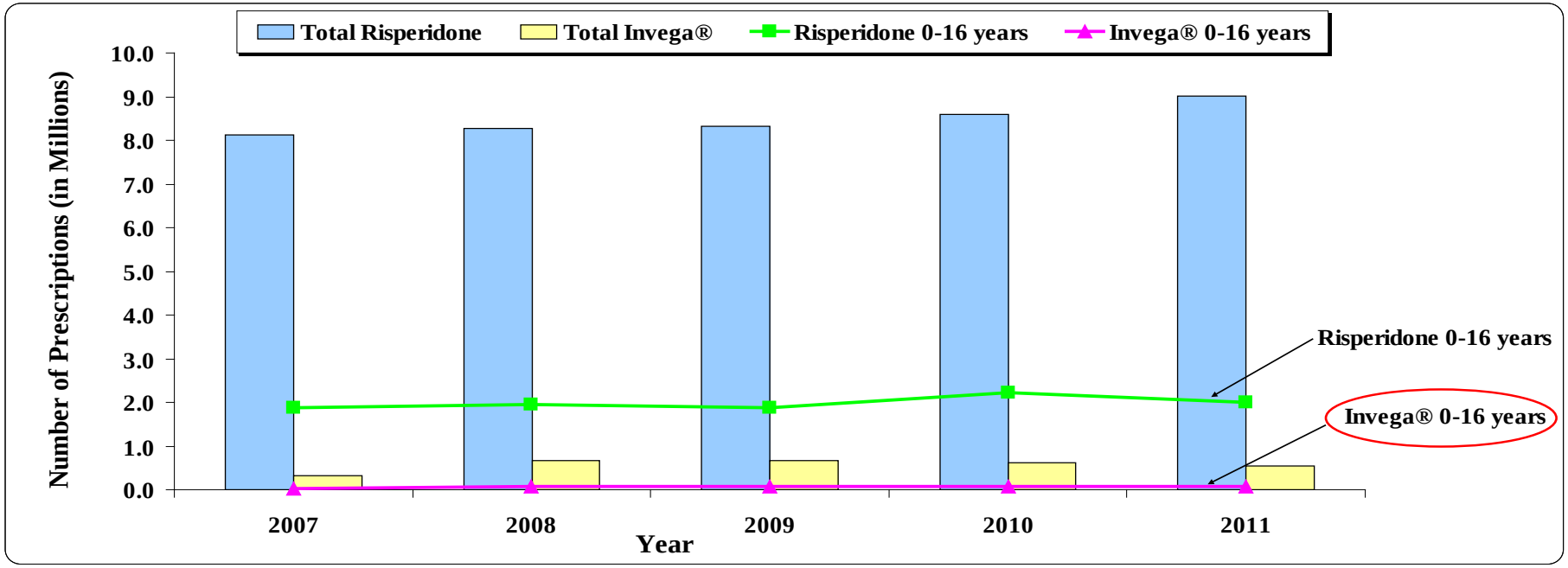
- **12.3 Clinical Pharmacology, Pharmacokinetics, Special Populations, Adolescents**
  - States that paliperidone systemic exposure in adolescents weighing ≥51 kg was similar to that in adults
  - In general, pharmacokinetics were comparable between weight groups, and age did not influence the paliperidone exposure

Pediatric Labeling Changes, continued
Invega® (paliperidone)

- **14.1 Clinical Studies, Schizophrenia, Adolescents**
  - Describes the adolescent efficacy study

Invega® (paliperidone) and Risperidone Pediatric Utilization

Nationally Estimated Number of Prescriptions for Invega® and Risperidone Dispensed to the Pediatric Population (0-16 years), from U.S. Outpatient Retail Pharmacies, 2007 - 2011



- 9 million risperidone prescriptions and 540,000 Invega® prescriptions were dispensed in 2011.
- The pediatric population (0-16 years) accounted for 22% (2 million) of risperidone prescriptions and 11.5% (62,000) of Invega® prescriptions.
- [1]IMS, Vector One®: National (VONA). Years 2007-2011. Data Extracted September 2012.

Invega® Drug Utilization, Prescriptions[1] and Patients[2] U.S. Outpatient Retail Pharmacy Setting January 2007 – June 2012, cumulative

	Prescriptions N	Share %		Patients N	Share %
INVEGA® TOTAL	**3,070,503**	***100.0%***		**431,387**	***100.0%***
0-16 years	**334,248**	***10.9%***		**46,562**	***10.8%***
0-5 years	3,448	*1.0%*		1,026	*2.2%*
6-11 years	116,019	*34.7%*		16,589	*35.6%*
12-16 years	214,782	*64.3%*		32,477	*69.7%*
17 years and older	**2,734,688**	***89.1%***		**389,163**	***90.2%***
Unspecified Age	**1,567**	***0.1%***		**430**	***0.1%***

*** Patient age subtotals** may not sum exactly due to patients aging during the study ("the cohort effect"), and may be counted more than once in the individual age categories. For this reason, summing across time periods or patient age bands is not advisable and will result in overestimates of patient counts.

[1]IMS, Vector One®: National (VONA). January 2007 through June 2012. Data Extracted September 2012.
[2]IMS, Total Patient Tracker (TPT). January 2007 through June 2012. Data Extracted September 2012.

Invega® Drug Utilization
Prescribing Specialty[1] and Diagnosis[2]
January 2007 – June 2012, cumulative

- Top prescribing specialty for Invega® was psychiatry (70% of prescriptions)
  - Pediatricians accounted for <1% of Invega® prescriptions
- Top diagnoses codes in pediatric patients by age
  - Patients aged 12-16 years: “Other Emotional Child Disorders”
  - Patients aged 6-11 years: “Attention Deficit Disorder”
  - Patients aged 0-5 years: *use too low to be able to capture diagnosis code data in physician survey data*

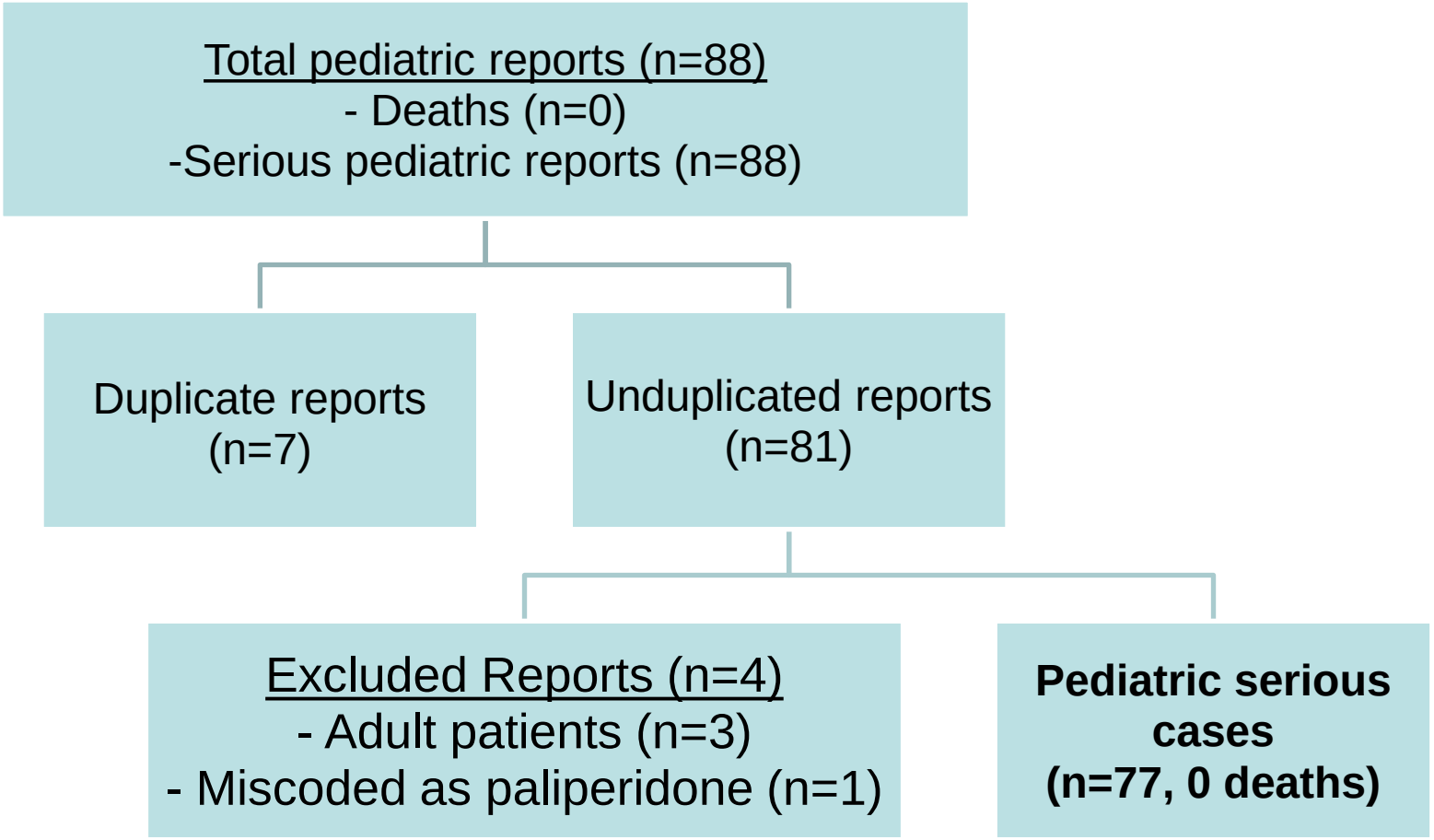
[1]IMS, Vector One®: National (VONA). January 2007 - June 2012. Data Extracted September 2012.
[2]Encuity Research, LLC., Physician Drug and Diagnosis with Pain Panel. January 2007 - June 2012. Data Extracted September 2012.

Total Number* of Paliperidone Adverse Event Reports Since Pediatric Approval
(Dec. 19, 2006 to June 30, 2012)

	All reports (US)	Serious**(US)	Death (US)
Adults (≥ 17 yrs.)	2130 (1314)	1345 (538)	113 (47)
Pediatrics (0-16 yrs.)	153 (127)	88 (62)	0 (0)
Unknown Age (Null values)	1139 (888)	481 (232)	48 (20)***
All Ages	3422 (2329)	1914 (832)	161 (67)

*May include duplicates and have not been assessed for causality
**Serious adverse drug experiences per regulatory definition (CFR 314.80) include outcomes of death, life-threatening events, hospitalization (initial or prolonged), disability, congenital anomaly and other serious important medical events.
***No pediatric cases identified

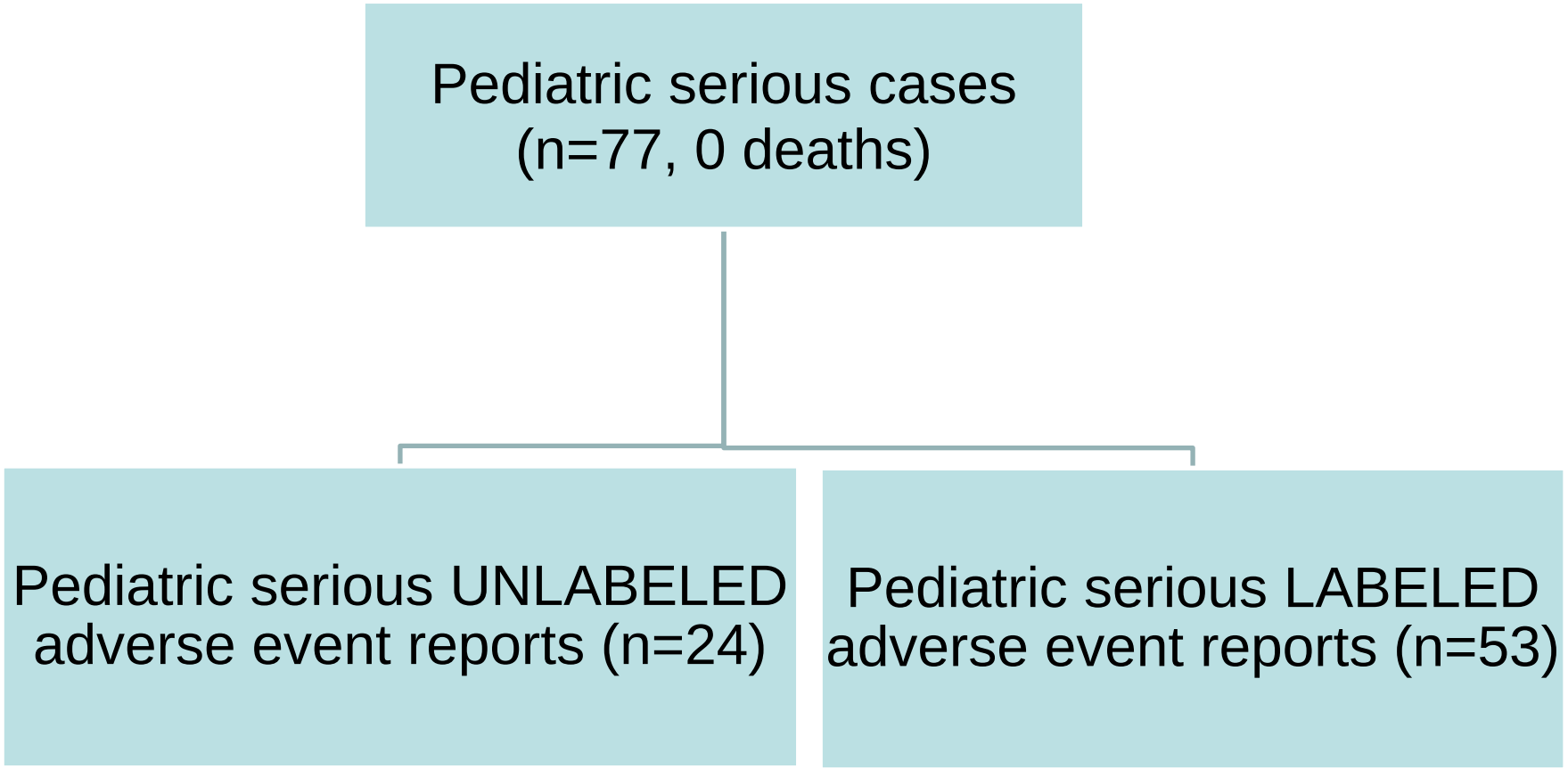
Selection of Serious Pediatric AERS Cases



Characteristics of Serious Pediatric Cases paliperidone (n=77)

- Gender known (n=76)
  - Male (n=50)
  - Female (n=26)
- Age known (n=77)
  - 0-1 month (n=2)
  - 1 month-<2 years (n=0)
  - 2–5 years (n=13)
  - 6-11 years (n=22)
  - 12-16 years (n=40)

Selection of Serious Pediatric AERS Cases



Serious Non-Fatal Unlabeled Adverse Events Invega® (paliperidone) (n=24)

- The unlabeled pediatric adverse event cases were
  - confounded by comorbidities or concomitant medications labeled for the adverse event, or
  - provided insufficient information to assess relationship between paliperidone and the events, or
  - were accidental exposures

Serious Non-Fatal Unlabeled Adverse Events Invega® (paliperidone) (n=24)

- Psychiatric (n=8)
- Accidental Exposure (n=7)
- Nervous System (n=2)
- Metabolic (n=2)
- Cardiac (n=1)
- Ocular (n=1)
- Renal (n=1)
- Reproductive (n=1)
- Vascular (n=1)

Serious Non-Fatal Unlabeled Adverse Events: Psychiatric (n=8) Invega® (paliperidone)

- Aggression/Belligerence (n=6)
- Depression (n=1)
- Disorientation (n=1)

- All events may have been associated with the underlying psychiatric illness or confounded by concomitant medications labeled for these events.

Serious Non-Fatal Unlabeled Adverse Events: Aggression/Belligerence (n=6), Invega® (paliperidone)

- 6 year-old male with history of violence, ADHD#, and "probable" bipolar disorder. He experienced aggression* and suicidal ideation while taking paliperidone 6 mg (unspecified frequency and duration) to treat ADHD, and 10 days after his concomitant lisdexamfetamine was switched to dexmethylphenidate. Dexmethylphenidate dose was increased, divalproex was started, and paliperidone was continued. Outcome unspecified. Lisdexamfetamine and dexmethylphenidate are labeled for an association with aggression.

#Attention Deficit Hyperactivity Disorder

*Unlabeled adverse events are underlined on this and subsequent case description slides

Serious Non-Fatal Unlabeled Adverse Events: Aggression/Belligerence (n=6), continued Invega® (paliperidone)

- Males, 8 and 11 years old, experienced defiance (coded as aggression) and irritability after starting paliperidone 3-6 mg daily to treat disruptive behavioral disorder (and bipolar disorder in the 11 year-old). In both cases paliperidone was withdrawn and risperidone, which they had previously been on, was restarted. Concomitant medications were not reported.
  - 8 year-old: The "adverse events were not as pronounced"
  - 11 year-old: Patient recovered

Serious Non-Fatal Unlabeled Adverse Events: Aggression/Belligerence (n=6), continued Invega® (paliperidone)

- 10 year-old female, with a history of "possible" bipolar disorder, experienced aggression and suicidal ideation while receiving paliperidone 3 mg daily for post-traumatic stress disorder. Paliperidone was continued and patient had not recovered. Concomitant medications included valproate, which is labeled for an association with aggression.

Serious Non-Fatal Unlabeled Adverse Events: Aggression/Belligerence (n=6), continued

Invega® (paliperidone)

- 15 year-old male was taking paliperidone 3 mg daily and aripiprazole to treat schizoaffective disorder, and concomitant desmopressin nasal spray for bed-wetting. At an unspecified time patient refused his medication, became belligerent and was hospitalized. Aripiprazole is labeled for an association with aggression.

Serious Non-Fatal Unlabeled Adverse Events: Aggression/Belligerence (n=6), continued Invega® (paliperidone)

- 16 year-old male experienced aggression, frustration, anger and violence 25 days after starting paliperidone 6-12 mg (frequency unspecified) to treat schizophrenia. He was hospitalized due to aggression, paranoia, and auditory hallucinations. Paliperidone was continued. Concomitant medications: lorazepam and benztropine. Lorazepam is labeled for an association with aggression.

Serious Non-Fatal Unlabeled Adverse Events: Accidental Exposure (n=7), Invega® (paliperidone)

- Age range: 2-5 years (Median of 2 years)
- Most serious case:
  - 2 year-old female opened her mother's bottle and ingested five 3-mg paliperidone tabs (15 mg total). Child was treated at ER with activated charcoal, admitted to PICU for overnight observation. Discharged next day.
  - Father reported failure of the child-resistant mechanism, "Sometimes the cap worked and locked properly, other times it spun right open."
- Labeling provides information on overdosage
  - supportive care

Serious Non-Fatal Unlabeled Adverse Events: Nervous System: Tics (n=2) Invega® (paliperidone)

- 5 year-old male with a history of Tourette's syndrome and ADHD[#] experienced a re-emergence of tics, and also profuse sweating when running, oculogyria, somnolence, fatigue, increased appetite, swollen face, orthostatic hypotension, and weight gain. Concomitant medications: pimozide, reboxetine, risperidone, and sertraline.
- 7 year-old male experienced tics in his head and neck, finger "tumor" treated with outpatient surgery, bones in back "crunch and crack like an old man", "violence" and "growling". Paliperidone stopped after approximately 3 years. Patient recovered from tics.

[#]Attention Deficit Hyperactivity Disorder

Serious Unlabeled Adverse Events, Continued Invega® (paliperidone)

- Metabolic (n=2)
  - Hypothyroidism (n=1)
  - Decreased blood glucose (n=1)
- Cardiac (n=1)
  - Myocarditis
- Ocular (n=1)
  - "Increased diopter", weight increase
- Renal (n=1)
  - Acute renal failure
- Reproductive (n=1)
  - Multiple complaints including swollen prostate
- Vascular (n=1)
  - Deep vein thrombosis

Serious Non-Fatal Labeled Adverse Events Invega® (paliperidone) (n=53)

- Central Nervous System (n=25)
- Metabolic (n=7)
- Psychiatric (n=6)
- Endocrine (n=4)
- Immunologic (n=4)
- Miscellaneous (n=7)
  - Neonatal withdrawal syndrome (n=2)
  - Overdose (n=2)
  - Priapism (n=2)
  - Rash (n=1)

Serious Non-Fatal Labeled Adverse Events Invega® (paliperidone)

Key:

- CI = Contraindications
- WP = Warnings and Precautions
- AR = Adverse Reactions
- USP = Use in Specific Populations
- OD = Overdosage

Central Nervous System Adverse Events (n=25)		Labeling				
		CI	WP	AR	USP	OD
Extrapyramidal symptoms (n=13)						
	Dystonia (n=8)			√		
	General extrapyramidal symptoms (n=3)			√	√	√
	Tardive dyskinesia (n=2)		√	√		
Neuroleptic malignant syndrome (n=6)			√	√		
Convulsion (labeled as seizure) (n=5)			√	√		√
Somnolence (n=1)				√	√	√

Serious Non-Fatal Labeled Adverse Events, cont. Invega® (paliperidone)

Labeled Adverse Event		Labeling				
		CI	WP	AR	USP	OD
Metabolic (n=7)						
	Weight gain (n=6)		√	√		
	Diabetes mellitus (n=1)		√			
Psychiatric (n=6)	Self-injurious behavior (captured under suicide) (n=2)		√	√		
	Suicide attempt (n=2)		√	√		
	Agitation (n=1)			√	√	
	Cognitive disorder (n=1)		√	√		

Key:

- CI = Contraindications
- WP = Warnings and Precautions
- AR = Adverse Reactions
- USP = Use in Specific Populations
- OD = Overdosage

Serious Non-Fatal Labeled Adverse Events, cont. Invega® (paliperidone)

Labeled Adverse Event		Labeling				
		CI	WP	AR	USP	OD
Endocrine (n=4)						
	Hyperprolactinemia – Gynecomastia (n=3)		√	√		
	Hyperprolactinemia – Amenorrhea (n=1)		√	√		
Immunologic (n=4)						
	Hypersensitivity (n=2)	√				
	Swollen tongue (n=1)			√		
	Urticaria (captured under hypersensitivity) (n=1)	√				

Key:

- CI = Contraindications
- WP = Warnings and Precautions
- AR = Adverse Reactions
- USP = Use in Specific Populations
- OD = Overdosage

Serious Non-Fatal Labeled Adverse Events, cont. Invega® (paliperidone)

Miscellaneous Labeled Adverse Events (n=7)	Labeling				
	CI	WP	AR	USP	OD
Neonatal withdrawal syndrome (n=2)				√	
Overdose (n=2)					√
Priapism (n=2)		√	√		
Rash (n=1)			√		

Key:

- CI = Contraindications
- WP = Warnings and Precautions
- AR = Adverse Reactions
- USP = Use in Specific Populations
- OD = Overdosage

Summary Pediatric Focused Safety Review Invega® (paliperidone)

- This concludes the pediatric focused safety review.
- No ***new*** pediatric safety concerns were identified.
- FDA recommends returning to routine monitoring.
- Does the Committee concur?

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Back Up Slides

Invega® (paliperidone) Adolescent Dosing: Schizophrenia Indication

- The recommended starting dose: 3 mg daily.
- Information on dose increases, if necessary, provided.
- Labeling states there was no clear enhancement to efficacy at the higher doses, while adverse events were dose-related.

Invega® (paliperidone) Mean Change in Body Weight, Adolescent Data

Mean change in body weight (kg) and the proportion of subjects with ≥7% gain in body weight from a placebo-controlled 6-week study in adolescents with schizophrenia

	Placebo	1.5mg/day	3mg/day	6mg/day	12mg/day
	N=51	N=54	N=16	N=45	N=34
Weight (kg) Change from baseline	0.0	0.3	0.8	1.2	1.5
Weight gain ≥7% increase from baseline	2%	6%	19%	7%	18%